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Pharmacological properties of betrixaban

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Venous thromboembolism (VTE) in acute medically ill patients is a leading cause of in-hospital morbidity and mortality. A majority of these VTE events occur post-discharge, and patients remain at increased VTE risk for up to 3 months post-discharge. Recent clinical trials of extended-duration thromboprophylaxis with enoxaparin, rivaroxaban, and apixaban in acute medically ill patients did not demonstrate a net clinical benefit compared with in-hospital thromboprophylaxis, and were shown to be associated with higher risks of major bleeding. Betrixaban is a new direct oral anticoagulant (DOAC) with a different pharmacokinetic profile than other DOACs. Betrixaban has the longest half-life among the DOAC class, with a terminal half-life of 35–45 h and an effective half-life of 19–27 h. Betrixaban has a low peak-to-trough ratio compared with other anticoagulants and a predictable duration of drug exposure, leading to overall consistent anticoagulant effect over 24 h. Betrixaban is mainly cleared via the hepatobiliary system and therefore not contraindicated in patients with severe renal insufficiency. Betrixaban was recently approved for the indication of extended thromboprophylaxis in the United States based on the APEX trial of betrixaban 80 mg once daily for 35–42 days compared with low molecular weight heparin enoxaparin for 10 ± 4 days in hospitalized acute medically ill patients. This study demonstrated that extended-duration betrixaban reduced VTE compared with standard-duration enoxaparin in acute medically ill patients, without increased risk of major bleeding. This patient population at risk of VTE may benefit from extended prophylaxis, ensuring continuum of care from in-hospital to post-discharge.

Introduction

Acute medically ill patients are at risk of venous thromboembolism (VTE), a leading potentially preventable cause of in-hospital morbidity and mortality in Europe and the United States (US).[1–3] Patients remain at risk for up to 3 months after hospital discharge, with the highest risk period within the first 6 weeks after discharge.[4] Preventative measures to reduce the risk of VTE events while hospitalized or after surgery include physical activity, intermittent pneumatic compression, and prophylactic doses of anticoagulants.[2] Until 2017, parenteral anticoagulants including low molecular weight heparins (LMWH), unfractionated heparins, or fondaparinux for 10 ± 4 days were the only recommended drugs for thromboprophylaxis for acute medically ill patients.[5] Notably, it has been demonstrated in observational studies that in-hospital prophylaxis alone does not protect patients against post-discharge VTE events.[6]

Recent clinical trials have investigated whether acute medically ill patients may benefit from extended-duration thromboprophylaxis, i.e. 4 to 6 weeks after discharge, with the LMWH enoxaparin as well as rivaroxaban and apixaban.[7–9] In those trials, extended anticoagulant therapy was not associated with a net clinical benefit compared with standard-duration (10 ± 4 days) thromboprophylaxis administered while hospitalized, and extended thromboprophylaxis with enoxaparin, rivaroxaban, or apixaban was associated with a higher risk of major bleeding.[7–9]

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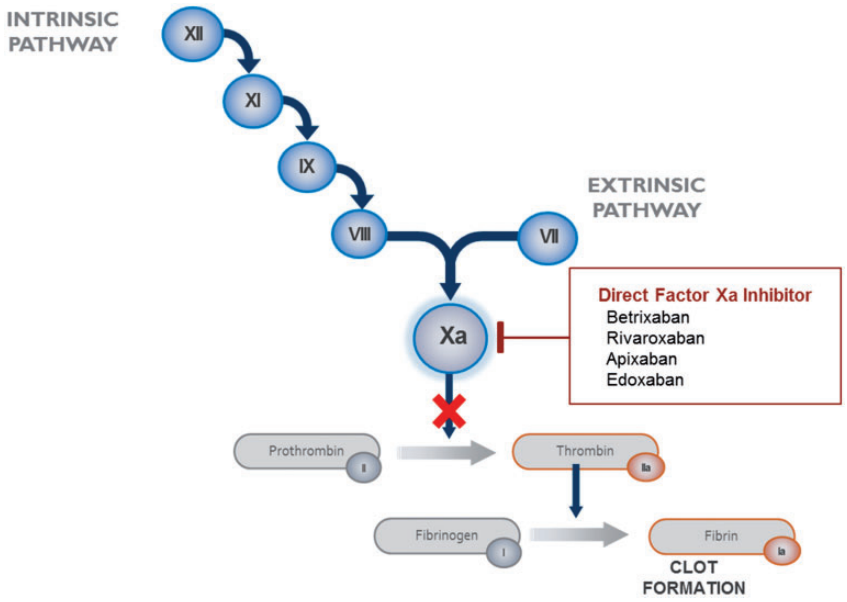

Figure 1 Coagulation cascade.[17] XII, factor XII; XI, factor XI; IX, factor IX; VIII, factor VIII; VII, factor VII; Xa, factor Xa.

Table 1 Pharmacokinetic and pharmacodynamic properties of direct oral anticoagulants[18,19]

	Betrixaban	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Thrombin
Half-life (h)	19-27	12	10-14	5-9	12-17
Dosing	o.d.	b.i.d.	o.d.	o.d. (b.i.d.)	b.i.d.
T_{max} (h)	3-4	1-3	1-2	2-4	2
Bioavailability (%)	34	50	62	66	7
Renal excretion (%)	17.8[a]	25	35	66	>80
Faecal excretion (%)	85[b]	46.7-56	62.2	26.4	82-88
CYP450 metabolism	No	Yes	No	Yes	No

b.i.d., twice daily; o.d., once daily; T_{max}: time to reach peak concentration in plasma after oral dose.
[a]Unchanged betrixaban in urine following an intravenous betrixaban dose.
[b]Following oral administration of radio-labelled betrixaban.

Betrixaban is a direct oral anticoagulant (DOAC) that directly inhibits factor Xa, with a different pharmacokinetic (PK) profile than other DOACs. The APEX study compared betrixaban at a dose of 80 mg once daily for 35 to 42 days with the standard-duration LMWH enoxaparin (at a dose of 40 mg once daily) for 10 ± 4 days in hospitalized acute medically ill patients.[10] This study demonstrated that extended prophylaxis with betrixaban led to a reduction in VTE compared with standard-duration enoxaparin, without an increase in major bleeding. Clinical results for betrixaban, including reduced rehospitalization rates,[11] are reviewed in further detail in article 3 of this supplement.[12]

Pharmacodynamics

Betrixaban competitively and reversibly inhibits free and prothrombinase-bound factor Xa in a concentration-dependent manner.[9,13-15] It has a profound selectivity for factor Xa above other serine proteases, including thrombin, and does not require a cofactor (such as anti-thrombin III) for activity.[13,16] In intrinsic and extrinsic coagulation pathways, factor Xa plays a central role in the cascade of blood coagulation for activation of prothrombin to thrombin (*Figure 1*).[13] Direct-acting inhibitors of factor Xa decrease thrombin generation, and thereby prevent clot formation.[13]

Pharmacokinetics

The pharmacology of betrixaban is distinct from that of other DOACs, including the lowest renal clearance and no metabolism by CYP enzymes (*Table 1*). At a dose of 80 mg, betrixaban is rapidly absorbed, and its plasma concentration peaks after 3-4 h. Bioavailability is 34% and is lowered if taken with fatty food. Betrixaban is less protein-bound (60%) than the other factor Xa inhibitors. Among DOACs, betrixaban has the longest half-life (*Table 1*), with a

terminal half-life of 35 to 45 h and an effective half-life of 19 to 27 h.[18] Betrixaban has a low peak-to-trough ratio and a predictable duration of drug exposure, leading to an overall consistent anticoagulant effect over 24 h.[18] For the 80-mg betrixaban doses, the anticipated C_{max} is 36 ng/mL, and the volume of distribution is ~32 L/kg. Betrixaban has slightly non-linear kinetics, which show that increasing doses are associated with greater than proportional increases in plasma concentrations.

Unlike apixaban and rivaroxaban, betrixaban is not metabolized by CYP enzymes (<1%) and does not induce or inhibit cytochrome P450 (CYP450) activity, lowering the risk of adverse drug events or interactions during concomitant administration.[18] Drugs that alter or compete for CYP enzyme activity can change the PK of concurrent medications that are metabolized by CYP450 enzymes, including antibiotics (e.g. ciprofloxacin, metronidazole, trimethoprim/sulfamethoxazole, clarithromycin, erythromycin), antifungals (e.g. ketoconazole, nefazodone, itraconazole, fluconazole), anticonvulsants (i.e. carbamazepine, phenytoin, phenobarbital), and antihypertensives (e.g. verapamil, diltiazem), drugs that are often administered to acute medically ill patients.[20] In contrast, betrixaban is a substrate of P-glycoprotein.[18] Dedicated Phase 1 studies found elevated betrixaban exposure when coadministered with the strong P-glycoprotein inhibitors, such as ketoconazole.[19] A PK analysis of the population from the APEX study also confirmed that P-glycoprotein inhibitors increase betrixaban concentrations when coadministered, and a dose reduction to 40 mg is appropriate.[21]

A proportion of patients at risk for VTE have renal or hepatic insufficiency.[22] Betrixaban is primarily excreted in the gut (85%) through bile via the hepatobiliary system, as well as via the P-glycoprotein efflux pump, mostly unmetabolized.[18,19] Patients with hepatic impairment [defined as cirrhosis, bilirubin >2× upper limit of normal (ULN), or liver enzymes >3× ULN] should not receive betrixaban, and obstructive jaundice could also cause drug accumulation.[18] The low renal clearance of betrixaban (11% following oral administration of radio-labelled betrixaban; 17.8% of the absorbed dose was observed as unchanged betrixaban in urine following intravenous administration); however, creates the possibility of safe administration in patients with severe renal impairment, defined as a reduced glomerular filtration with creatinine clearance ≥15 to <30 mL/min.[19] Patients with severe renal insufficiency had higher plasma concentrations of betrixaban after full (80 mg) and half (40 mg) doses compared with patients with normal kidney function in the pivotal APEX trial.[23] However, increases in plasma concentration in this patient population were not associated with an increase in major bleeding at the 80 mg or 40 mg dose of betrixaban.[19,23] Therefore, the betrixaban label in the US supports use of betrixaban in patients with severe renal impairment (in contrast with other DOACs), but because these patients are still at increased risk of bleeding events, betrixaban dosage should be reduced to 40 mg.[19] Even so, decisions on initiation and type of thromboprophylaxis in acute medically ill patients with severe renal insufficiency need to be individually tailored.

Conclusion

Betrixaban, approved in the US for extended thromboprophylaxis in hospitalized acute medically ill patients at risk of VTE, is a new direct factor Xa inhibitor with pharmacological properties that make it particularly appropriate for the acute medically ill population: a long half-life, a low peak-to-trough concentration ratio, low renal clearance, and no metabolism by CYP enzymes. These properties have several important clinical implications for the population where adverse drug events due to renal impairment, comorbidities, and polypharmacy are considerable. Betrixaban has a consistent anticoagulant effect over 24 h, no contraindication in patients with severe renal insufficiency (dose reduction indicated), and a low propensity for drug–drug interactions (dose reduction indicated for patients on P-glycoprotein inhibitors).

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